Precise in vivo genome editing via single homology arm donor mediated intron-targeting gene integration for genetic disease correction.

Journal: Cell Res

Publication Year: 2019

Authors: Keiichiro Suzuki, Mako Yamamoto, Reyna Hernandez-Benitez, Zhe Li, Christopher Wei, Rupa Devi Soligalla, Emi Aizawa, Fumiyuki Hatanaka, Masakazu Kurita, Pradeep Reddy, Alejandro Ocampo, Tomoaki Hishida, Masahiro Sakurai, Amy N Nemeth, Estrella Nunez Delicado, Josep M Campistol, Pierre Magistretti, Pedro Guillen, Concepcion Rodriguez Esteban, Jianhui Gong, Yilin Yuan, Ying Gu, Guang-Hui Liu, Carlos Lopez-Otin, Jun Wu, Kun Zhang, Juan Carlos Izpisua Belmonte

PubMed link: 31444470

Funding Grants: CIRM Graduate Student Training Grant for the Implementation of a Stem Cell Technology and Lab Management Program: Training in Stem Cell Sciences and Regenerative Medicine

Public Summary:
In vivo genome editing represents a powerful strategy for both understanding basic biology and treating inherited diseases. However, it remains a challenge to develop universal and efficient in vivo genome-editing tools for tissues that comprise diverse cell types in either a dividing or non-dividing state. Here, we describe a versatile in vivo gene knock-in methodology that enables the targeting of a broad range of mutations and cell types through the insertion of a minigene at an intron of the target gene locus using an intracellularly linearized single homology arm donor. As a proof-of-concept, we focused on a mouse model of premature-aging caused by a dominant point mutation, which is difficult to repair using existing in vivo genome-editing tools. Systemic treatment using our new method ameliorated aging-associated phenotypes and extended animal lifespan, thus highlighting the potential of this methodology for a broad range of in vivo genome-editing applications.

Scientific Abstract:
In vivo genome editing represents a powerful strategy for both understanding basic biology and treating inherited diseases. However, it remains a challenge to develop universal and efficient in vivo genome-editing tools for tissues that comprise diverse cell types in either a dividing or non-dividing state. Here, we describe a versatile in vivo gene knock-in methodology that enables the targeting of a broad range of mutations and cell types through the insertion of a minigene at an intron of the target gene locus using an intracellularly linearized single homology arm donor. As a proof-of-concept, we focused on a mouse model of premature-aging caused by a dominant point mutation, which is difficult to repair using existing in vivo genome-editing tools. Systemic treatment using our new method ameliorated aging-associated phenotypes and extended animal lifespan, thus highlighting the potential of this methodology for a broad range of in vivo genome-editing applications.